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Drug Induced Hemolytic Uremic Syndrome: A Case Report.

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Abstract

Certain drugs can cause thrombotic micro-angiopathy through different mechanisms. In this report we describe a case of a 43-year-old female who developed hemolytic uremic syndrome after receiving multiple medications for menorrhagia. After a month of treatment with norethisterone, her symptoms did not improve and she presented to the emergency complaining of severe vaginal bleeding. Tranexamic acid and mefenamic acid were prescribed for symptomatic relief. Within 24 hours, she presented to the emergency again complaining of persistent vomiting. Her laboratory investigations revealed evidence of acute renal failure with hemolysis and thrombocytopenia. She was diagnosed with hemolytic uremic syndrome. Immediate management included plasma exchange, hemodialysis and blood transfusion. Her condition was stabilized but she did not recover her normal renal function and remained in the end stage renal failure category. This patient received three medications (Tranexamic acid, Norethisterone and Mefenamic acid) that are attributed to her diagnosis. Hemolytic uremic syndrome must be recognized early as it is associated with significant mortality and morbidity.

Introduction

There is a spectrum of drugs that have been reported to cause thrombotic micro-angiopathy syndromes. For example, quinine and antimicrobials such as trimethoprim-sulfamethoxazole have evidence for causing thrombotic micro-angiopathy in addition to chemotherapeutic agents [1]. Gemcitabine is one of the most common cancer therapies associated with this condition [2]. There are diverse mechanisms of which drugs result in these adverse reactions in particular. Some reports suggest acute immune-mediated reactions while others suggest dose or duration related toxic reactions [3].

Thrombotic micro-angiopathies manifest as either thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. They are pathologically characterized by occlusive micro-vascular thrombosis and clinically by micro-angiopathic hemolytic anemia and profound thrombocytopenia. Micro-angiopathic hemolysis occurs as red blood cells become fragmented as they pass through the thrombi within the microvasculature. Organ ischemia and subsequent failure may occur as a result of small-vessel thrombosis. The kidney is particularly susceptible to this thrombotic process in hemolytic uremic syndrome [4].

Here we report a case of a 43-year-old female who was receiving multiple medications for menorrhagia and eventually developed hemolytic uremic syndrome. These medications were tranexamic acid, mefenamic acid and norethisterone.

Case Presentation

A 43-year-old female with a past medical history of menorrhagia was prescribed norethisterone for around one month to help reduce heavy bleeding. She does not have any chronic diseases and she is not on other regular medications. She presented to the emergency room complaining of severe per vaginal bleeding. She had no other symptoms; her physical examination and laboratory investigations were unremarkable for any abnormality. After evaluation by the on call gynecology team, she was prescribed 1 gram of tranexamic acid along with 500 milligrams of mefenamic acid to be taken three times daily. Her condition was stabilized in the emergency and she was discharged home. After approximately 24 hours, she presented again to the emergency room with acute onset of persistent vomiting. She vomited food content multiple times prior to presentation. She did not have fever, diarrhea or any other symptoms. She was hemodynamically stable and her physical examination was unremarkable. Her laboratory investigations revealed a sharp elevation in serum creatinine and urea with a drop in hemoglobin and platelet count. The case was referred to internal medicine on call team for further evaluation. She was admitted to the ward with an impression of acute renal failure and hemolysis.

She had evidence of micro-angiopathic hemolytic anemia, renal failure and thrombocytopenia. Therefore, she was diagnosed with hemolytic uremic syndrome and an ultrasound guided core biopsy of left renal parenchyma was obtained to confirm the diagnosis. Typical HUS that is classically caused by shiga toxin was ruled out as her stool culture was negative and there were no diarrheal symptoms. Thrombotic thrombocytopenic purpura was excluded as her ADAMTS-13 activity was normal and she did not have neurological symptoms or fever.

The results of her investigations were as follows (Investigations time table and kidney biopsy pictures are attached at the end of the manuscript):

Peripheral blood smear showed marked microcytic hypochromic anemia with anisopoikilocytosis (Schistocytes 3%). Moderate polymorphnuclear leucocytosis with shift to left and cytoplasmic toxic granulations were noted along with absolute lymphopenia.

ADAMTS-13 antigen: 0.18 IU/ml (0.41-1.41) (Low)
ADAMTS-13 activity: 0.70 IU/ml (0.41-1.30) (Normal)
Antibodies against ADAMTS-13: 2.5 U/ml (<12 U/ml: Negative)
Anti-Phospholipid IGG Antibodies: 1.4 (<12: Negative)
Haptoglobin: 1.93 (Normal Range: 0.30-2.00)

Ultrasound Doppler of the renal vessels revealed poor renal parenchymal perfusion and high resistance index of inter lobar arteries. Findings were highly suggestive of acute renal parenchymal insult (Acute tubular Necrosis).

Mercaptoacetyltriglycine (MAG3) renal: The patient was injected with radioactive isotope tracer (3.62 mCi Tc-99m-MAG3). Scintigraphic picture of bilateral nephropathic changes were revealed to be significantly affecting the nephrons function of both kidneys with compromised overall effective renal plasma flow.

The patient's kidney biopsy was examined under electron microscopy: Thrombotic micro-angiopathy was discovered with cortical necrosis consistent with hemolytic uremic syndrome. The glomerulus revealed focal infarct with changes consistent with the diagnosis of thrombotic micro-angiopathy. Kidney biopsy histopathology results confirmed the same findings.

Management and Outcome

Immediate treatment plan included plasma exchange, hemodialysis and blood transfusion. The patient underwent five sessions of plasma exchange with 5% albumin in the first week. On her second day of admission, she was started on intravenous methylprednisolone 1 gram daily for three days followed by oral prednisolone. She had signs of fluid overload with poor urine output and her estimated glomerular filtration rate was below 15%. Hence, hemodialysis was initiated and continued regularly for around one month. She also received 4 units of packed red blood cells on different occasions due to low hemoglobin, with the lowest level being 6.7 mg/dL. Tranexamic acid, norethisterone and mefenamic acid were all discontinued on admission.

With all the aforementioned treatments, platelet count and hemolysis parameters were back to normal range with a significant improvement in urine output. However, her renal

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Table.1

Laboratory Investigations									
	Hb (12-16 g/dL)	WBC (4-11 x10^9/L)	Platelet (150 – 450 x10^9/L)	Urea (3-7 mmol/L)	Creatinine (49-90 umol/L)	Total/ Direct Bilirubin (< 18/0-5 umol/L)	ALT (30-65 u/L)	Reticulocyte Absolute (0.05-0.12 10^9/ml)	LDH (100-190 u/L)
First ER Visit	11.4	15.3	216	4.5	82	-	-	-	-
Second ER Visit	8.8	16.37	87	19.1	708	13.3/5.13	318	0.075	3578
24-Hours Following Admission	6.7	16.64	133	22.5	845	16.3/5.5	84	0.09	1468
After 5 sessions of plasma exchange	9.1	20	284	22.1	865	7.5/1.6	24	-	283

function did not improve and her eGFR remained below 15%. She was then kept under observation without hemodialysis. During this trial period she was maintaining hemodynamic stability without any clinical or laboratory abnormalities necessitating any medical intervention. She was categorized as having stage five chronic kidney disease . After extensive evaluation, she was discharged home with close follow up of renal function in nephrology clinic.

Discussion

This patient received three medications (Tranexamic acid, Norethisterone and Mefenamic acid) that are potentially attributed to developing thrombotic micro-angiopathy. We reviewed the literature and found case reports of non-steroidal anti-inflammatory drugs and progesterone having a causal association with TMA [5]. To the best of our knowledge, there are no case reports of tranexamic acid having this association.

Tranexamic acid is an anti-fibrinolytic drug, it forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin. It therefore reduces bleeding but, in certain situations, it may expose patients to a risk of thrombosis [6]. There are plenty of reports regarding the thrombotic adverse effects of tranexamic acid including deep vein thrombosis, pulmonary embolism, retinal vein, cerebral and arterial thrombosis [7]. There are no randomized controlled trials that assess the thrombotic risk of tranexamic acid as evidence is mainly supported by case studies. This case adds to the literature representing a causal association between tranexamic acid administration and thrombotic micro-angiopathy.

In addition to tranexamic acid, this patient received mefenamic acid which is a non-steroidal anti-inflammatory drug. It has been reported in the literature that NSAIDs can cause hemolytic uremic syndrome [5, 8].

She also received norethisterone for one month prior to developing hemolytic uremic syndrome. In a systematic review of published reports, progesterone was reported with a probable evidence for a causal association with thrombotic micro-angiopathy [5, 9].There is a reported case of hemolytic uremic syndrome following administration of norethisterone [10].

It is difficult to conclude whether this clinical sequela was an adverse reaction to one drug, a combination of two or all three of them. Etiologies of thrombotic-microangiopathy other than drug toxicity were excluded such as thrombotic thrombocytopenic purpura and shiga toxin-mediated hemolytic uremic syndrome [5]. Understanding the drugs' mechanism of action and the pathophysiology of hemolytic uremic syndrome can help delineate causal associations and outline potential serious side effects.

Conclusion

Physicians must be cautious when prescribing tranexamic acid, norethisterone and mefenamic acid as they may result in thrombotic micro angiopathy. Drug induced hemolytic uremic syndrome is a life-threatening condition that must be recognized early in order to achieve successful treatment outcomes.

Disclosure:

The authors of this manuscript have no financial support, funding or any conflict of interest to declare.

Ethics approval was obtained from the research department at King Hamad University Hospital.

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Kidney Biopsy